UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/807,736	03/24/2004	Tetsuji Okuno	4-30961BC1C1	5416

1095 7590 10/30/2006

NOVARTIS
CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
EAST HANOVER, NJ 07936-1080

EXAMINER	
KWON, BRIAN YONG S	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 10/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/807,736	OKUNO ET AL.	
	Examiner	Art Unit	
	Brian S. Kwon	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-18* is/are rejected.

7)☒ Claim(s) *12* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/989,577.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *05/12/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Priority

1. Certified copies of the priority documents, UK 9911926.5 filed 05/21/1999 and UK 9925131.6 filed 10/22/1999, have been received in Application No. 09/989,577.

Claim Objections

2. Claim 12 is objected, as being of improper dependent form for failing to further limit the subject matter of a cancelled claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

For the examination purpose, the claim 12 is interpreted as the dependent claim of the claim 11.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 11-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for reducing angiogenesis or treating the specific angiogenesis-induced disease (e.g., rheumatoid arthritis, osteoarthritis, breast cancer, colon cancer, small cell, lung cancer, prostate cancer, diabetic retinopathy, psoriasis, haemangioma, haemangioblastoma) with said bisphosphonate compound, does not reasonably provide enablement for "treatment of angiogenesis", "inhibiting basic fibroblast growth factor induced angiogenesis" or "inhibiting angiogenesis". The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

The instant claims are drawn to a method for inhibiting angiogenesis comprising administering said bisphosphonate compound, namely zoledronic acid, or a pharmaceutically acceptable salt thereof or a hydrate thereof alone or in combination with a vascular endothelial growth factor inhibitor.

The specification defines the term "angiogenesis" as "the formation of new blood vessels" that is an essential event in may physiological processes such as wound repair, ovulation, embryogenesis and many pathological events such as inflammation, myocardial ischemia, rheumatoid arthritis, osteoarthritis and tumor formation.

Websters II Dictionary defines the term "inhibit' as "prevent; and "prevent" as "anticipate or counter in advance, to keep from happening".

The interpretation of the instant invention (with "broadest reasonable interpretation") allows for the prevention, complete cure, eradication or total elimination of angiogenesis, more specifically many pathological events such as wound repair, ovulation, embryogenesis, inflammation, myocardial ischemia, rheumatoid arthritis, osteoarthritis, diabetic retinopathy, pain, age-related macular degeneration and metastasis of tumor (e.g., breast cancer, colon cancer, lung cancer, prostate cancer, haemangioblastoma, haemangioma) by the administration of said compounds.

With respect to the scope of enablement for "treatment of angiogenesis",

As discussed above, the scope of the instant "angiogenesis" encompasses multitude of physiological conditions and/or pathological conditions related to new blood vessel formation in the body including wound repair, ovulation, embryogenesis, myocardial ischemia, rheumatoid arthritis, osteoarthritis, diabetic retinopathy, psoriasis, haemangioblastoma, haemangioma, pain, macular degeneration, breast cancer, lung cancer, prostate cancer, colon cancer, infectious disease, obesity, restenosis, atherosclerosis, neointimal formation, neurodegeneration, hypertension and etc...

The relative skill of those in the art of pharmaceuticals and the unpredictability of the pharmaceutical art is very high. Although the angiogenesis involves in many physiological processes and many pathological events, it is not known yet that a single underlying mechanism ties together the multiple complex disorders having unrelated manifestations encompassed by the instant claims. Especially in the cancer art, there are

no known compounds of similar structure which have been demonstrated to treat all types of tumour formation. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "silver bullet" is contrary to our present understanding of oncology. Cecil Textbook of Medicine states that "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004). Different types of cancers affect different organs and have different method of growth and harm the body. Also see In re Buting, 163 USPQ 689 (CCPA 1969), wherein 'evidence involving a single compound and two types of cancer, was held insufficient to establish the utility of the claims directed to disparate types of cancers'. Thus, it is beyond the skill of oncologists today to get an agent to be effective against all cancers or cancers due to an angiogenesis.

As discussed above, the claims are very broad due to the complex nature of the disease condition which often involves multiple factors. Therefore, the skill artisan would turn to undue amount of trial and error to find out which disease would be responsive to the administration of said bisphosphonates.

The specification discloses assays in vitro and vivo and provides that said bisphosphonates exhibit anti-angiogenic property and shows potential therapeutic utility in treating osteoarthritis, breast cancer, lung cancer, bone cancer, hepatic and diaphragm metastasis (Examples). However, there is no demonstrated correlation that the tests and results apply to the claimed therapeutic utility embraced by the instant claims.

Since the efficacy of using said bisphosphonates in treating conditions medicated angiogenesis (including physiological processes such as wound repair, ovulation or

embryogenesis as well as pathological events such as inflammation, myocardial ischemia, rheumatoid arthritis, osteoarthritis, tumor formation and etc...) mentioned above cannot be predicted from a priori but must be determined from the case to case by painstaking experimental study and when the above factors are weighed together, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to use the invention commensurate in scope with the claims.

With respect to the scope of enablement for "inhibiting angiogenesis",

There are no known compounds of similar structure which have been demonstrated to prevent or cure all types of angiogenesis or pathological conditions associated with angiogenesis. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "silver bullet" is contrary to our present understanding of pharmacology. Cecil Textbook of Medicine states that "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004). For example, different types of cancers affect different organs and have different method of growth and harm the body. Also see In re Buting, 163 USPQ 689 (CCPA 1969), wherein 'evidence involving a single compound and two types of cancer, was held insufficient to establish the utility of the claims directed to disparate types of cancers'.

Contrary to the applicant's invention, the state of art does not recognize the administration of any compounds or compositions to prevent or completely eliminate (cure) the angiogenesis, for example rheumatoid arthritis, osteoarthritis and tumor

formation (see "Reumatoid Arthritis Treatments", Johns Hopkins Center, www.hopkins-arthritis.com, 2006; "Osteoarthritis: no cure, but many options for symptom relief", Mckinney et al., Cleve Cln J Med, 2000, abstract, Vol. 67, No. 9, pp. 665-71; "Lung cancer: small cell", Medline Plus, www.nlm.nih.gov, 2006; "Bone Cancer", www.plwc.org, 2005). Thus, it is not understood how one skilled in the art can reasonably establish the basis and the type of subject to which the instant compounds can be administered in order to have the "prevention" or completely cure or eradication effect.

The relative skill of those in the art of pharmaceuticals and the unpredictability of the pharmacy art is high. The specification does not provide any competent evidence or disclosed tests that are highly predictive for the preventive utility of the instant compounds.

The specification discloses assays in vitro and vivo and provides that said bisphosphonates exhibit anti-angiogenic property and shows potential therapeutic utility in treating osteoarthritis, breast cancer, lung cancer, bone cancer, hepatic and diaphragm metastasis (Examples). However, there is no demonstrated correlation that the tests and results apply to the claimed preventive utility embraced by the instant claims.

Since the efficacy of the claimed compound(s) in inhibiting (preventing) said angiogenesis mentioned above cannot be predicted from a priori but must be determined from the case to case by painstaking experimental study and when the above factors are weighed together, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to use the invention commensurate in scope with the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

4. Claim 16 is rejected under 35 U.S.C. 102(b) as being anticipated by Katdare (WO 95/29679).

Katdare teaches the use of bisphosphonates (e.g., pamidronate, alendronate, risedronate, etc...) for the treatment or prevention of tumour metastasis (e.g., metastatic bone disease) and arthritis (page 6, lines 15-33; page 10, lines 15-19).

Although Katdare is silent about "inhibiting basic fibroblast growth factor induced angiogenesis", such feature must be inherently presented in the referenced method of treating or preventing metastatic bone disease. The prior art directing the administration of bisphosphonates inherently possessing a therapeutic effect for the same ultimate purpose as disclosed by Applicants anticipates Applicants claim even absent explicit recitations of the mechanism of action.

5. Claims 16-17 are rejected under 35 U.S.C. 102(e) as being anticipated by Askew et al. (US 6048861).

Askew teaches the use of composition comprising integrin receptor antagonist, bisphosphonates (e.g., alendronate, pamidronate, etc...) and a vascular endothelial growth factor inhibitor for the treatment, prevention or inhibition of angiogenesis, macular degeneration, inflammation, diabetic retinopathy, atherosclerosis and tumor growth (abstract; column 34, lines 27-31 and claim 26).

Since the interpretation of the instant claims allow for the inclusion of any other unspecified ingredients even in major amounts in said composition, the reference anticipates the claimed invention.

Although Askew is silent about "embolism-causing amount" or "inhibiting basic fibroblast growth factor", such feature must be inherently presented in the referenced method of treating, prevention or inhibition of angiogenesis. The prior art directing the administration of bisphosphonates inherently possessing a therapeutic effect for the same ultimate purpose, for the treatment or prevention of angiogenesis, as disclosed by Applicants anticipates Applicants claim even absent explicit recitations of the mechanism of action.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 11-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Askew et al. (US 6048861).

The teaching of Askew has been discussed in above 35 USC 102(e) rejection.

The reference differs from the claimed invention in intra-arterial administration. However, the determination of dosage delivery system having optimum therapeutic index is well considered within the skill of the artisan, and the artisan would be motivated to determine optimum dosage delivery system to achieve maximum therapeutic effects of the drug. Thus, the reference makes obvious the claimed invention.

7. Claims are rejected under 35 U.S.C. 103(a) as being unpatentable over Askew et al. (US 6048861) and further in view of Reszka et al. (US 6416964 B2).

The teaching of Askew has been discussed in above 35 USC 102(e) rejection. However, Askew is silent about the use of zoledronic acid or zoledronate for the claimed utility.

Reszka teaches zolendronate as functional equivalent of alendronate and pamidronate that is useful in the treatment or prevention of angiogenesis, macular degeneration, inflammation, diabetic retinopathy, atherosclerosis and tumor growth (column 1, lines 16-26; column 1, lines 56-59; column 1, line 65 thru column 2, line 3; column 2, lines 28-48; column 6, lines 32-42; column 7, line 49 thru column 10, line 29).

One having ordinary skill in the art would have been motivated to select the claimed compound with the expectation that substitution of zoldronate for alendronate or pamidronate would not significantly alter the analogous properties of the compound of the reference due to their known functional equivalency in the art. One would have been motivated to combine these references and make the modification because they are drawn to same technical fields (constituted with same ingredients and share common utilities), and pertinent to the problem which applicant concerns about. MPEP 2141.01(a).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims 11-16 are rejected provisionally under the judicially created doctrine of double patenting over claims 9-10 of the copending application No. 10/484,482, claims 17-26 of the copending application No. 10/10/276,623 or 1, 5-11 and 15-18 of the copending application No. 10/10/531,677.

Although the conflicting claims are not identical, they are not patentably distinct from each other.

Since the proliferative disease such as prostate carcinoma, lung cancer and melanoma in the copending application'482, the bone metastases in the copending application'623 and the atherosclerosis in the copending application'677 "metes and bounds" the instantly claimed "angiogenesis", the copending application(s) make/makes obvious the instant invention.

With respect the instantly claimed intra-arterial administration, such determination of dosage delivery system having optimum therapeutic index is well considered within the skill of the artisan, and the artisan would be motivated to determine optimum dosage delivery system to achieve maximum therapeutic effects of the drug. Thus, the reference makes obvious the claimed invention.

Conclusion

9. No Claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (571) 272-0581. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached on (571) 272-0718. The fax number for this Group is (571) 273-8300.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications may be obtained from Private PAIR only. For more information about PAIR system, see http://pair-direct.uspto.gov Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Brian Kwon
Primary Patent Examiner
AU 1614